

HEART TRANSPLANTATION

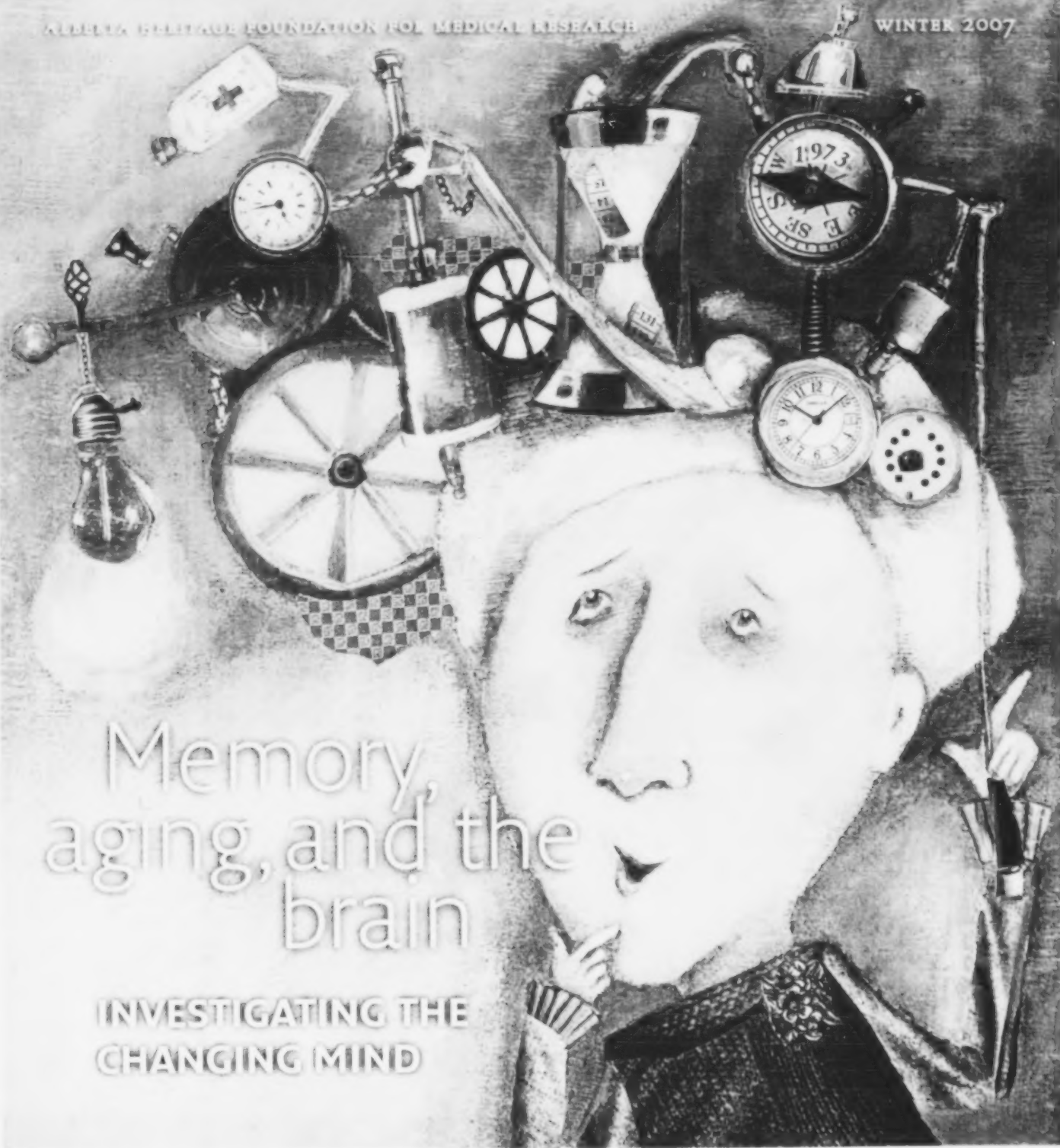
THE INSULIN MYSTERY

COMMUNITY AND OLDER ADULTS

ResearchNews

ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

WINTER 2007



Memory,
aging, and the
brain

INVESTIGATING THE
CHANGING MIND



On the cover

Cover artist **Kyrsten Brooker** was born in Illinois and grew up in Edmonton. After graduating from the design/illustration program at Brooklyn's Pratt Institute she spent eight years in Brooklyn building a client list that included *The*

New York Times, *Sports Illustrated*, *Psychology Today*, and The Walt Disney Company. Kyrsten returned to Edmonton in 1997 where she now lives with her husband and two young sons. Since moving back to Edmonton she has illustrated ten children's books.

AHFMR MISSION

AHFMR supports a community of researchers who generate knowledge, the application of which improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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Contents

WINTER 2007

FEATURES

6 Understanding transplantation: *the heart of the matter*

Dr. Lori West's passion for pediatric cardiology and research has brought her to Edmonton, where she has set her sights on further improving the field of transplantation.

8 Heart-felt research

Research that began with a quest to understand some basic mechanisms in heart cells has opened up the possibility of new treatments for life-threatening abnormal heart rhythms.

10 The insulin mystery

How insulin is regulated in a healthy person may hold insights for research on type 2 diabetes.

COVER STORY

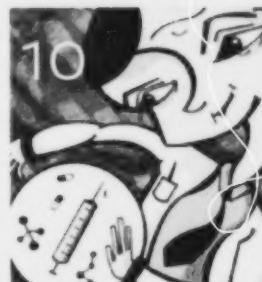
12 Memory, aging, and the brain

Many of us fear that our brains will somehow fail us as we get older. AHFMR researchers are investigating the science behind some of our worst fears—age-related memory loss and Alzheimer's.

22 Community, collaboration, and older adults

Aging "in place", in your own neighbourhood, is finally becoming a real choice thanks to a Calgary program.

6



22

The AHFMR magazine is published four times annually and is distributed free of charge to a controlled circulation list within Canada. If you wish to receive it, please contact us by phone, e-mail, fax or by letter. It is also on the web at www.ahfmr.ab.ca.

© Contents copyright of AHFMR.
ISSN 1700-6236 (print) ISSN 1703-5694 (online)
Canadian Publications Agreement #40064910

Return undeliverable Canadian addresses to:

AHFMR 1500, 10104-103 Avenue
Edmonton, AB T5J 4A7



IN EVERY ISSUE

2
**VOICES FROM
THE COMMUNITY**
Almost every major news story or public-policy issue today has a scientific angle. How do non-scientists find their way through the debate?

3
COOL TOOLS
Take a look at some of the cutting-edge equipment used by AHFMR researchers.

4
**RESPONDING
TO THE READER**
A reader asks if there is any new research on essential tremor and how it affects the brain.

24
**RESEARCHERS
IN THE MAKING**
How does language help children learn about their world?

26
FOLLOWING UP
Check in with two clinical dietitians on their work to prevent eating disorders in children.



Production Notes

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Design: Lime Design Inc.

Cover and feature illustrations: Krysten Brooker
Photography and illustration: Trudie Lee, Brian Harder, Calgary; Laughing Dog Photography, Edmonton; Amanda Woodward, Edmonton; Getty Images

AHFMR Research News is printed by grafikom
Speedfast on Pacesetter Matte Text 70 lb.

From the President's desk



We are delighted to introduce the first issue of the newly redesigned *Research News* magazine. After nearly seven years in its previous format, AHFMR's publication

was ready for a fresh look and some new content. Our little magazine's audience has doubled, growing from a small publication to one that reaches more than 28,000 Albertans. It was time to evolve to better serve our readers.

The biggest change is that the magazine is now full colour inside as well as out, making *Research News* more reader-friendly and even more visually appealing. If you're concerned about the cost, you might be surprised to hear that the change amounts to only about 3 cents more per issue.

In response to feedback from readers, we've also added two new regular features. *Following Up* checks in with investigators previously featured in the magazine, to see what has been happening with their research. *Cool Tools* profiles some of the high-tech equipment that health and biomedical researchers use in their work.

Our goal is to do the best possible job of communicating to the public the results of Albertans' ongoing investment in health research. As always, we welcome your questions and story ideas, and it's helpful to find out what you like and don't like. Contact us at the address on the opposite page and let us know what you think of the new *Research News*!

Kevin Keough, Ph.D., FCAHS
President and CEO
Alberta Heritage Foundation
for Medical Research



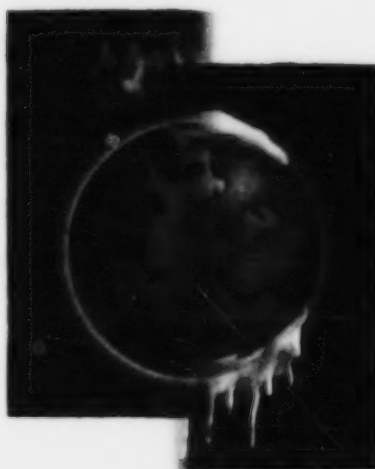
Science, non-science, and nonsense

Almost every major news story or public-policy issue today has a scientific angle. How do non-scientists find their way through the debate? Why does it matter? Physicist and science commentator Dr. Lawrence Krauss explains.

■ IF YOU'VE READ A NEWSPAPER, watched the news, or listened to the radio in the past few years, you've certainly read or heard about global warming. Perhaps one of the defining public-policy issues of our time, the subject has sparked tremendous controversy as citizens and governments around the world struggle to come to terms with the threat of catastrophic climate change due to carbon dioxide emissions. But the controversy is artificial to some extent, according to Dr. Lawrence Krauss.

The renowned physicist and science commentator uses the issue to illustrate the tensions between journalism and science. "Journalists are trained that there are two sides to every story, that they need to provide balance," he says. "But in science, most of the time one side is wrong—the balance doesn't exist."

He points out that the evidence linking rising levels of greenhouse gases to retreating glaciers is clear. And this evidence allows scientists to predict a disastrous future unless we act immediately to reduce greenhouse gases. Temperatures



"In science, most of the time one side is wrong"

will increase, water levels will rise substantially—and a billion people could be displaced by the effects. Yet, even though the data behind these predictions are beyond doubt, the media have to find somebody who disagrees, in order to balance their stories. "But that one person who disagrees might represent only himself, while the other side represents the scientific consensus," says Dr. Krauss. The result? The issue becomes muddled. The public becomes confused. Governments do not act.

But, in a democratic society, shouldn't everything be open to debate? Absolutely, says Dr. Krauss. Except that, when it comes to science, there is an unambiguous way to identify nonsense: experiment. You propose something, and you test it. If the test results don't bear out your proposition, you throw out the theory—you don't continue to debate its merits. He points out that people used to argue about whether the earth was round or flat. But scientific experiment proved it to be round and the subject no longer needs to be debated. The opposing side does not need to be included in newspaper articles.

So how do we, as citizens, distinguish between science and nonsense? Healthy skepticism is one way, according to Dr. Krauss. "Ask yourself some sensible questions about whether something seems reasonable and, if it doesn't seem reasonable based on those sensible questions, it probably isn't."

However, this ability to differentiate requires at least a little scientific training—something with which fewer

There is an unambiguous way to identify nonsense: experiment

and fewer people are equipped. "Many journalists aren't comfortable with science issues. People who like to think of themselves as intellectuals often proudly proclaim their scientific illiteracy. And in the US, more than 90% of middle-school science teachers have no post-secondary training whatsoever in science."

The fallout is that people who aren't properly informed can't vote appropriately; and legislators can't make wise policy decisions on issues of fundamental importance to all of us—issues such as global warming. "The scientist can be vital to the proper functioning of society," he concludes. *

DR. LAWRENCE KRAUSS is a professor of physics and astronomy, and director of the Center for Education and Research in Cosmology and Astrophysics at Case Western Reserve University in Cleveland, Ohio. He is an internationally renowned scientist, writer, and commentator on science and society. The author of several popular science books, including *The Physics of Star Trek*, Dr. Krauss is a contributor to *The New York Times*, and a regular guest on radio and television programs. AHFMR invited him to Alberta recently to deliver a public lecture entitled *Science, Non-Science and Nonsense: From Aliens to Creationism, and from Government to the Classroom*.



A U of A staffer demonstrates the Bod Pod

The BodPod

AT FIRST GLANCE, you might think a giant egg had been laid in the Human Nutrition Research Unit at the University of Alberta. But it's the BOD POD Body Composition Tracking System: a fast, accurate, and safe tool that uses air displacement to measure body composition. When subjects sit in the sealed chamber they hear a click, a whirring noise, and a loud pop, then feel a slight change of pressure as the machine gets to work measuring the amount of air they displace. Then a computer takes that measurement and calculates the fatty mass and fat-free mass of the subject. The entire test takes five to ten minutes.

Researchers from a variety of fields will use this new piece of equipment, one of only a few in Canada. Dr. Linda McCargar (supported through the Health Research Fund which AHFMR administers for Alberta Health and Wellness) investigates the effects of diet and exercise on body composition, fat distribution, and energy metabolism. AHFMR Population Health Investigator Dr. Geoff Ball develops and evaluates weight-management programs for overweight children and youth. Both will use the BOD POD to assess changes in subjects' body composition. Cancer researchers will use the equipment to investigate how well patients are preserving lean mass while undergoing cancer therapy. *

The Bod Pod is for research purposes only and is not available for public use.



Essential tremor

A reader asks about new research on essential tremor and how it affects the brain. Dr. Zelma Kiss responds.

About this column

AHFMR frequently receives letters requesting information about Heritage research or about various medical conditions. "Responding to the Reader" is a *Research News* feature intended to provide up-to-date information related to readers' questions, with the help of experts in the Alberta research community. AHFMR cannot provide medical advice, however; please see your family physician about your specific health concerns.



PARKINSON'S DISEASE, ESSENTIAL TREMOR, AND DYSTONIA are movement

disorders with symptoms that can be particularly cruel.

Parkinson's is a chronic, degenerative brain disease that affects every aspect of daily living. Symptoms such as tremor, stiffness, and slowness of movement appear gradually but get worse over time. Sufferers may eventually have difficulty walking, talking, or completing simple tasks. It is estimated that over 100,000 Canadians have *Parkinson's*, and another 500,000 are affected, directly or indirectly, by the disease.

Many more Canadians suffer from other neurological movement disorders.

Dystonia is one of these, characterized by involuntary muscle contractions, which force certain parts of the body into

abnormal, sometimes painful, movements or postures. The most common movement disorder, however, is *essential tremor*. Many people with this condition do not seek medical help, although it can reach a severe stage where the sufferer

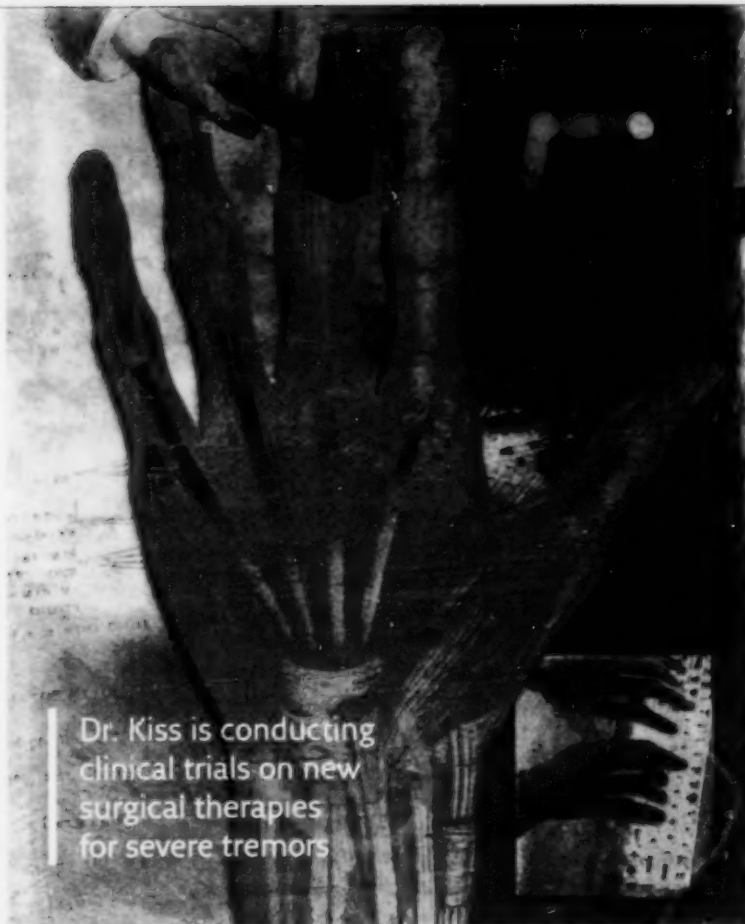
cannot stop shaking. Essential tremor was once called "familial benign tremor" because it sometimes runs in families.

A reader with a family history of essential tremor recently asked if there is any new research on its cause and on how tremors affect the brain.

Heritage Clinical Investigator Dr. Zelma Kiss is a Calgary researcher and neurosurgeon who specializes in helping patients with essential tremor and *Parkinson's* disease, as well as individuals with epilepsy, and certain psychiatric disorders. Scientists have not yet found the exact cause of *Parkinson's* disease or essential tremor, says Dr. Kiss, adding that more research in this area is definitely needed. In some cases there is a strong family history, but generally there is no way to predict who will be affected, as the genetic abnormality has not yet been identified.

"Tremor" is an uncontrollable rhythmic movement caused by involuntary muscle contraction. Tremors can be mild or severe, and can vary in severity during a 24-hour period or from day to day. An individual with tremor will shake and may move back and forth. Sufferers often worry about appearing odd;

The most common movement disorder is essential tremor



Dr. Kiss is conducting clinical trials on new surgical therapies for severe tremors

embarrassed, they may withdraw from social interaction.

There are different types of tremor. Essential tremor generally affects the hands but it may affect other parts of the body as well, such as the head, neck, or trunk. It can also cause the voice to quiver. In some cases, the tremor occurs only when the individual is in certain positions (for example, with hands outstretched)—this is called *postural tremor*. In others, the shaking may be triggered by specific movements, which is known as *action-specific tremor*. In Parkinson's disease, on the

other hand, tremor typically occurs while the individual is at rest.

"Tremor can be one of these movement disorders, or it may be related to other neurologic conditions, such as multiple sclerosis or, very rarely, brain-stem lesions," says Dr. Kiss. "It can take time to determine the right diagnosis; it's not always straightforward. So it's important to consult a neurologist or a specialist in movement disorders."

Dr. Kiss is conducting clinical trials on new surgical therapies for severe tremors. She

uses a technique called *deep brain stimulation* that involves surgically implanting an electronic device into the patient's brain. Similar to a pacemaker, the device uses stimulation to block the brain signals that cause tremor. Dr. Kiss leads a team investigating how this brain stimulation works.

The standard treatment for essential tremor is medication (beta blockers, anticonvulsants, or benzodiazepines). In severe cases, the doctor may recommend surgery to stop the tremor; neurosurgeons will operate on a very small area deep within the brain, called the *thalamus*. *

About the researcher

Dr. Zelma Kiss is an *AHFMRClinical Investigator* and an assistant professor at the University of Calgary, in the Department of Clinical Neurosciences and the Hotchkiss Brain Institute.

Selected publication

Anderson TR, Hu B, Iremonger KJ, Kiss ZHT. Selective attenuation of afferent synaptic transmission as a mechanism of thalamic deep brain stimulation induced tremor arrest. *Journal of Neuroscience* 2006 Jan 18;26(3):841-850.

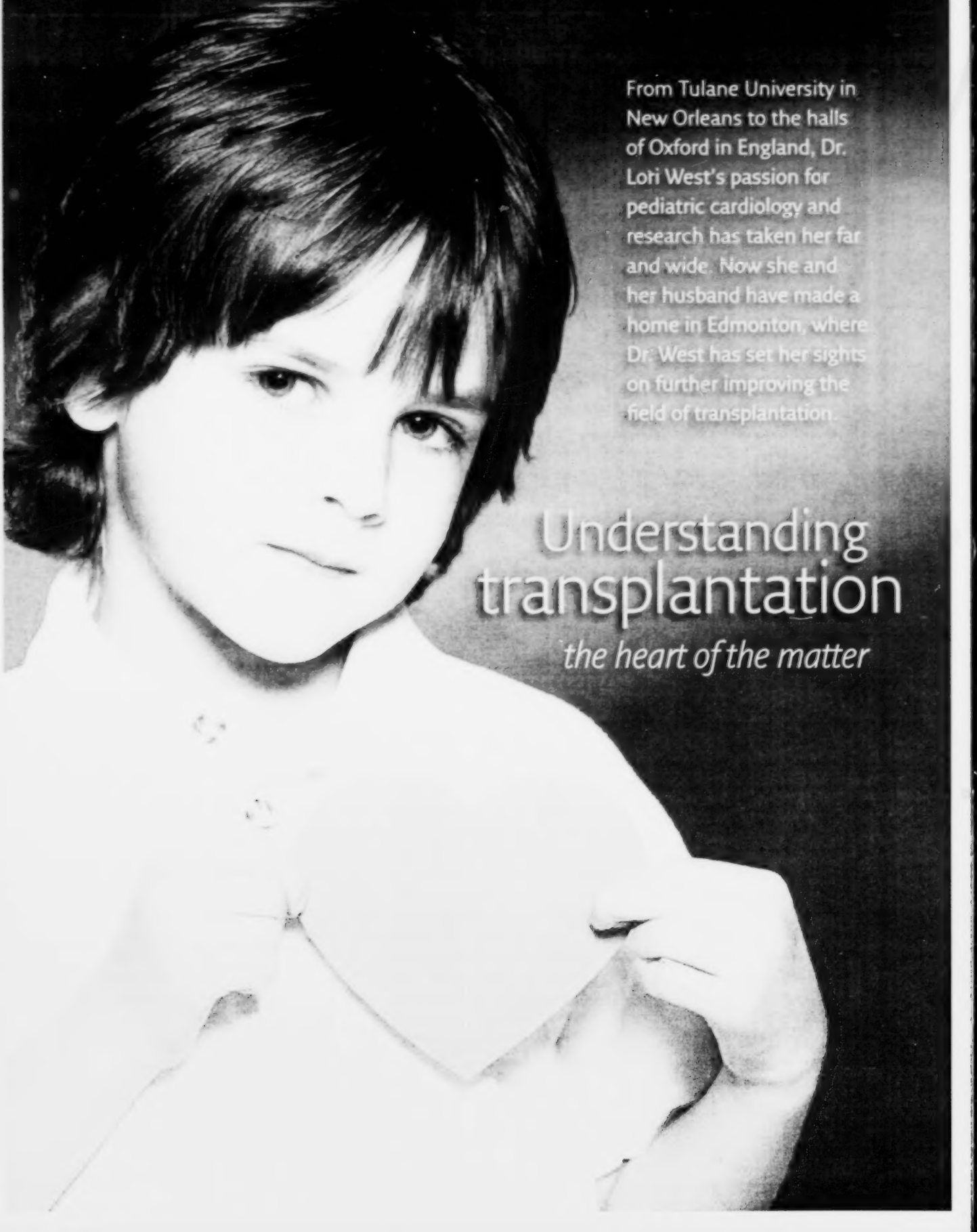
Recommended websites

International Essential Tremor Foundation

<http://www.essentialtremor.org/>

Parkinson Society Canada

<http://www.parkinson.ca>



From Tulane University in New Orleans to the halls of Oxford in England, Dr. Lori West's passion for pediatric cardiology and research has taken her far and wide. Now she and her husband have made a home in Edmonton, where Dr. West has set her sights on further improving the field of transplantation.

Understanding transplantation

the heart of the matter



AHFMR SENIOR SCHOLAR DR. LORI WEST has a busy career—not only as a cardiologist, but also as a researcher. Now director of the new Heart Transplantation Research Program at the University of Alberta, Dr. West addresses the whole range of issues affecting heart-transplant patients. Dr. West is no stranger to setting up a program of this magnitude. She was recruited to Alberta because of her success with a similar program at the Hospital for Sick Children in Toronto.

A UNIQUE PERSPECTIVE
DR. WEST works all along the continuum from bench to bedside, from research to care.

"As a clinician I take care of patients who have problems that I don't always have solutions for, patients waiting for heart transplants, for example," says Dr. West. "The research lab is where we investigate the questions for which we don't have answers. The resulting research, we hope, will lead to answers and solutions that can solve these problems. We could then use this information to improve care." This approach applies to all aspects of the transplantation process, from understanding why a body might reject a heart to how transplant complications impact patients and their families.

Studying transplantation from these different angles requires collaborating with a variety of healthcare professionals ranging from physicians to scientists to social workers, and many others. The collaborative spirit of this endeavour excites Dr. West. "Many programs and institutes outside of our own have shown an interest in working together to improve the face of transplant medicine. There is such enthusiasm for collaborating here, and it is really refreshing."



Babies can receive hearts from donors with incompatible blood types

PAST SUCCESSES
THIS FULL-CIRCLE APPROACH to care has worked for Dr. West in the past. She has made some important discoveries

regarding organ rejection and heart transplants in babies. Using information gleaned from the laboratory, Dr. West and her colleagues discovered that the infant immune system, being still immature, is not held in check by the same parameters as the adult immune system.

"We began to look at some of the rules and regulations that govern heart transplantation, and one of them was blood type," she explains. "You always make sure that your donor and recipient are compatible. However, research we did in the lab helped us realize that the things which make that barrier impossible to cross in adults are not present in babies."

This discovery meant that babies could receive hearts from donors with incompatible blood types—something that had never been considered. It removed one of the obstacles preventing a baby from receiving a new heart.

Dr. West is quick to say that there are still many other complications when it comes to pediatric heart transplants. She thinks that understanding why the body accepts or rejects an organ will likely be accomplished in small steps. With her new team at the University of Alberta, Dr. West is certain to take some of those steps and advance the field of transplant medicine.



About the researcher

AHFM Senior Scholar **Dr. Lori West**

is a full professor in the Department of Pediatrics at the University of Alberta, as well as an adjunct professor in the Department of Surgery and the Department of Medical Microbiology and Immunology. She is also director of the Heart Transplantation Research Program.

Selected publication

Fan X, Ang A, Pollock-BarZiv SM, Douchand AJ, Ruiz P, Wilson G, Platt J, West LJ. Donor-specific B-cell tolerance after ABO-incompatible infant heart transplantation. *Nature Medicine*. 2004 Nov;10(11):1227-1233.

Heart-felt research

Research that began with a quest to understand the basic mechanisms involving calcium in heart cells has opened up the possibility of new treatments for life-threatening abnormal heart rhythms.

Ever since 1986, when the *Journal of Biological Chemistry* published a paper by a team of scientists from the University of Alberta, researchers have been working to understand the basic mechanisms involving calcium in heart cells.

■ CALLED THE *cardiac ryanodine receptor (RyR2)*—less formally, the calcium-release channel—this protein controls the release of calcium ions from the *sarcoplasmic reticulum*, a specialized structure in the cell that contains large stores of calcium. The release of calcium ions from the sarcoplasmic reticulum is an essential step in the muscle contraction that produces a heartbeat.

Sometimes things go wrong with calcium handling in cardiac cells. For some 30 years scientists have known that spontaneous calcium release within the cell can cause the muscle contractions which trigger extra heartbeats. The mechanism behind these triggered *arrhythmias* (abnormal heart rhythms) remained a mystery.

Dr. West is quick to say that there are still many other complications when it comes to pediatric heart transplants. She thinks that understanding why the body accepts or rejects an organ will likely be accomplished in small steps. With her new team at the University of Alberta, Dr. West is certain to take some of those steps and advance the field of transplant medicine. *



About the researcher

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is a full professor in the Department of Pediatrics at the University of Alberta, as well as an adjunct professor in the Department of Surgery and the Department of Medical Microbiology and Immunology. She is also director of the Heart Transplantation Research Program.

Selected publication

Fan X, Ang A, Pollock-BarZiv SM, Dipchand AI, Ruiz P, Wilson G, Platt JL, West LJ. Donor-specific B-cell tolerance after ABO-incompatible infant heart transplantation. *Nature Medicine* 2004 Nov;10(11):1227-1233.

Heart-felt research

Research that began with a quest to understand the basic mechanisms involving calcium in heart cells has opened up the possibility of new treatments for life-threatening abnormal heart rhythms.

FOR THE PAST 12 YEARS OR SO, Heritage Scientist Dr. Wayne Chen and his team have studied a protein that is responsible for the release of calcium within heart cells.

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Sometimes things go wrong with calcium handling in cardiac cells

Enter Dr. Chen's research on the ryanodine receptor. His first breakthrough came when he followed up on an Italian group's identification of a mutation in the ryanodine receptor gene. The mutation causes a very rare genetic condition called *catecholaminergic polymorphic ventricular tachycardia* (CPVT). Individuals with this abnormality seem fit and healthy, but they can experience arrhythmias during physical activity or acute emotion—arrhythmias which often cause sudden cardiac death.

"We wondered how this mutation could cause sudden cardiac death in CPVT," says Dr. Chen. "We found that the mutation reduces the threshold for spontaneous calcium release from the sarcoplasmic reticulum when a person is

under stress. The spillover sets in motion a chain of events that causes an arrhythmia. We've published several papers outlining our theory, and it has sparked a lot of interest worldwide. This is gratifying, but for us it's not the end of the story. CPVT affects only a very small number of people. I believe the theory can explain a lot more."

In particular, Dr. Chen wants to expand his theory to include the arrhythmias that are a leading cause of sudden death in people with heart failure, itself a major cause of hospitalization and death in Canada. Dr. Chen believes that abnormal functioning of the ryanodine receptor leads to spontaneous calcium release when a person with heart failure experiences additional stress. This suggests that the ryanodine receptor could be a

therapeutic target in the treatment of both cardiac arrhythmias and heart failure.

Since 2004, Dr. Chen has been working with University of Calgary chemistry professor Dr. Tom Back to develop drugs that suppress spontaneous calcium release. They have tested about 20 drugs and have identified three candidates to date.

"Our theory on the role of the ryanodine receptor is just a beginning," notes Dr. Chen. "That's why we're working on a number of projects to further strengthen evidence for the theory. We're testing existing drugs and developing new drugs. We're using animal models to see whether animals have the same defect.

"When I started this work, I wasn't thinking about the clinical problems of heart failure. I was totally involved in figuring out how the ryanodine receptor works. But as we've made progress on the basic understanding, I've become more and more interested in applying that knowledge to solve the clinical problems. I think we're onto something really exciting and important." *



About the researcher
AHFMR Scientist
Dr. Wayne Chen

is a full professor in the Department of Physiology & Biophysics and the Department of Biochemistry & Molecular Biology in

the University of Calgary's Faculty of Medicine. He is a member of the Libin Cardiovascular Institute of Alberta.

Selected publication

Jiang D, Xiao B, Yang D, Wang R, Choi P, Zhang L, Cheng H, Chen SRW. RyR2 mutations linked to ventricular tachycardia and sudden death reduce the threshold for store-overload-induced Ca^{2+} release (SOICR). *Proceedings of the National Academy of Sciences of the United States of America* 2004 Aug 31;101(35):13062-13067.

The insulin mystery

Diabetes results from a problem with insulin secretion. But how is insulin regulated in a healthy person?

SOMETIMES THINGS JUST SEEM TO FALL INTO PLACE. Ask diabetes researcher and AHFMR Scholar Dr. Patrick MacDonald, one of the youngest people ever to be awarded a prestigious Canada Research Chair. Dr. MacDonald had originally considered becoming a physician, but a fourth-year undergraduate research project on testosterone gave him a taste for lab work, and he has never looked back. Now Edmonton, already at the forefront of diabetes research, will benefit. The city's reputation for groundbreaking diabetes research and an offer of support from AHFMR were big factors in his recent decision to accept a faculty position at the University of Alberta.

■ DR. MACDONALD completed his Ph.D. in Toronto, then went to Sweden for a post-doctoral fellowship, followed by another at Oxford. "When I left for Europe, Edmonton had already established itself as a centre for diabetes research," he says. "I knew I'd come back to Canada, so Edmonton was always in the back of my mind."

The young scientist investigates type 2 diabetes (often called adult-onset diabetes), which



"Edmonton had already established itself as a centre for diabetes research"

accounts for about 80% of cases. The disease usually affects older people who are overweight, but nowadays is increasingly being found in obese children. Obesity often results in *insulin*

resistance, whereby muscle tissue and fat tissue do not respond properly to insulin. "Normally, if someone becomes obese and insulin-resistant,

Dr. MacDonald wants to understand how the beta cells work

the pancreatic beta cells [which produce insulin] have a very high capacity to compensate," says Dr. MacDonald. "It's when they fail to compensate that people get type 2 diabetes."

Although we know that type 2 diabetes results from a problem with insulin secretion, he explains, we don't understand the nature of the problem. "But perhaps more importantly, we really don't know how insulin release is regulated in the healthy condition. So before we can figure out what the problem is in diabetes, we need to understand how things work under normal circumstances."

Dr. MacDonald wants to understand, therefore, how the beta cells work. By studying the electrical excitability of the cells, he examines how they release insulin in response to glucose. He explains that when blood sugar goes up, the pancreatic beta cells fire electrical signals in the same way nerves and muscles do. This electrical activity is linked to the release of insulin in a relationship called *stimulus-secretion coupling*. "In your brain, electrical activity is coupled to information transmission; in your muscles it's coupled to contraction; in pancreatic beta cells, electrical activity is coupled to the release of insulin," he explains.

Dr. MacDonald also studies the fine detail of how insulin exits the cell. "In the beta cells, insulin is stored in little balls, ready to be released when the cell receives a stimulus," he

says. "These little balls fuse with the membrane of the cell and spit insulin out." Understanding more about how this process works could help identify the dysfunction which results in diabetes. The knowledge could also help identify new targets for drugs.

Dr. MacDonald is looking forward to contributing to Edmonton's reputation for diabetes research and working with other researchers in various fields. The construction of the Health Research Innovation Facility, which will house the Alberta Diabetes Institute, is bound to facilitate this collaboration. "It will bring all sorts of diabetes research into one building—clinical research, nutrition and exercise, transplantation, and, on my side of things, the basic research," says Dr. MacDonald. "It's a unique opportunity to interact with people in different aspects of health research. I think it's going to be fantastic." ❖



**About the researcher
Dr. Patrick**

MacDonald is an *AHFMR Scholar* and an assistant professor in the Department of Pharmacology at the University of Alberta. He also holds the Canada Research Chair in Islet Biology.

Quick Facts

In type 1 diabetes, the body makes too little or no insulin. In type 2 diabetes, the body can't use the insulin it does make.

Source: Canadian Diabetes Association

AHFMR has contributed \$20 million toward the construction of the Health Research Innovation Facility at the University of Alberta. The facility will provide laboratory space for hundreds of researchers and students. It is scheduled to open in October 2007.


Selected publications

MacDonald PE, Braun M, Galvanovskis J, Rorsman P. Release of small transmitters through kiss-and-run fusion pores in rat pancreatic β -cells. *Cell Metabolism* 2006 Oct;4:283-290.

Recommended website

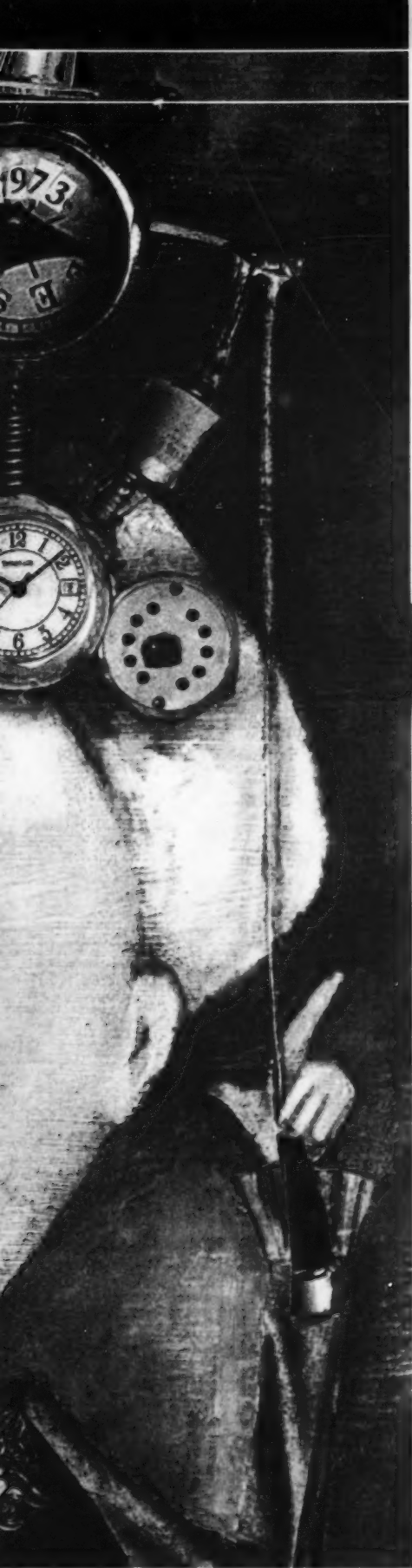
Dr. Patrick MacDonald's web site

<http://www.bcell.org>



Memory, aging, and the brain

What if that misplaced car key's a minor slip of an indicator to bigger trouble ahead? Many of us fear that possibility will somehow fall us as we get older. The sobering story profiled in this issue by researchers who have spent the last few decades behind some of our worst fears may relate memory loss and Alzheimer's



LISTEN IN

on any group of aging baby boomers, and at some point there's bound to be talk about health concerns. Cancer, heart disease, and diabetes are all threats as we get older. But more often than not, one concern overrides all others—the ravages of Alzheimer's disease and other dementias.



DR. ROBERT
SUTHERLAND

■ “MEMORY is a central piece to an enjoyable old age,” says Heritage Scientist Dr. Robert Sutherland, director of the Canadian Centre for Behavioural Neuroscience at the University of Lethbridge. “Individuals who have lost their memory are desperate people. They are adrift. They have lost themselves. It's no surprise that memory problems of old age are a very serious concern for many of us.”

The bad news is that memory naturally deteriorates with age. But there's good news too. Researchers are learning more about how memories are formed and where they are stored; and this knowledge brings opportunities to develop therapies to correct memory deficits.

THE FOUNDATIONS OF MEMORY

ONE OF THE KEY BREAKTHROUGHS SO FAR is an understanding of the biological basis for memory: a lasting change in the connections between *neurons* (nerve cells in the brain). “This is a physical reality,” says Dr. Sutherland. “It's what permits you to tell me what you had for breakfast.” Memory decline is associated with the weakening and loss of these strong connections between groups of neurons. The process by which these connections develop is called *synaptic plasticity*. It's one of the important neurochemical foundations of both memory and learning. (*Read more about synaptic plasticity on page 16.*)

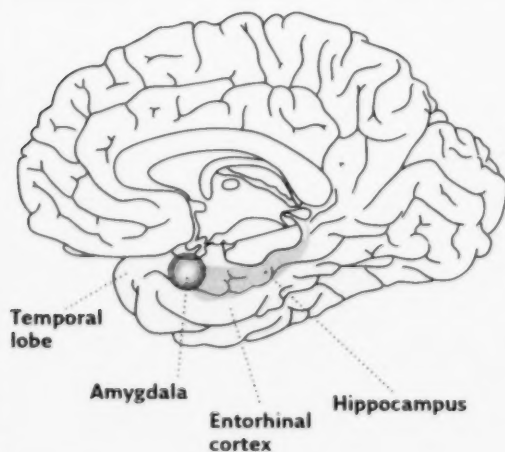
Of the many memory systems in the brain, the core system that allows you to consciously recollect is located in the *hippocampus*. This structure is found in both the left and right hemispheres of the *cerebral cortex*, near the base of the brain. If you put your finger just above your ear, the hippocampus is a few centimetres away from your fingertip.

What's going on in the brain at this time?

Researchers generally agree that the hippocampus is essential to the process called *episodic memory*, the memory system that forms new memories about experienced events—such as this morning's breakfast.

"The neurons in the hippocampus are specifically tuned to quickly make changes in their connections to other neurons," explains Dr. Sutherland. "They are stripped down metabolically and do minimal housekeeping, because their main focus is altering the connection strength. This makes them vulnerable to assault: from illness, infection, short periods of oxygen loss, stress, drugs—even a bump on the head." Unfortunately, almost any damage to these neurons will send them into a death cycle, or at least make them very sick. This explains why problems with episodic memory are among the first to appear in any chronic condition, from depression to Alzheimer's. (Read about an Alberta-based research project on Alzheimer's on page 20.)

MAPPING OUT THE BRAIN



"In a sense, aging is an accumulation of sub-threshold 'hits,'" notes Dr. Sutherland. The damage done by each assault accumulates over time, leaving a record in the hippocampus and

making it more susceptible to other assaults.

Fortunately, memory doesn't rely entirely on the hippocampus. Memory patterns (*schemas*) are kept in safe storage elsewhere in the cortex. "This is what is adaptive about old age," notes Dr. Sutherland. "We may lack the detail of what we had for breakfast or where we were a week ago, but memory systems that are stored permanently allow us to recognize situations and respond on that basis. Once you have the knowledge, it's there independently of your hippocampus." (Find out more about memories in the hippocampus and other areas of the brain on page 18.)

MEMORY DECLINE

DR. SUTHERLAND STUDIES the role of the hippocampus in both rodents and humans. One aspect he looks at is *age-related memory decline*. In general, memory that depends on the hippocampus starts to decline in rats and humans around the beginning of what we call "middle age". What's going on in the brain at this time?

Dr. Sutherland and his team have observed decreases in the size of the hippocampus with age, as well as declining levels of certain neurochemicals. They determined that the size change almost perfectly corresponds to the slowdown in adult *neurogenesis* (the creation of neurons). The hippocampus is the only part of the adult cerebral cortex where stem cells produce new neurons. In young rats hundreds of new neurons are added every day; but by the time rats begin to have problems with episodic memory—at an age equivalent to 70 in humans—only a few new neurons are being added every day.

Dr. Sutherland points out that, although few neurons are being produced, it isn't because the stem cells have died; they have simply become dormant, and research in rats has shown that these stem cells can be stimulated to become active again. If you take an old rat and start it exercising, or put it in an interesting new envi-

Memory systems

Declarative memory is the aspect of human memory that stores everyday events and factual knowledge. It is generally considered to have two main sub-categories:

Episodic memory is the function that stores specific events that we have personally experienced and allows us to remember them in their original context.

Semantic memory is the system that stores concepts, facts about the world, and skills we have acquired.

ronment, the stem cells will start working again. Dr. Sutherland has also succeeded in stimulating stem cells by injecting certain growth factors.

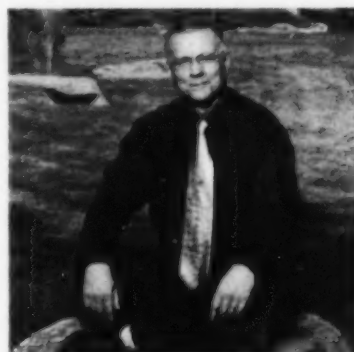
"I think this is a very fruitful avenue of research—trying to discover what factors, internal and external, can maintain stem cells. Right now we have some preliminary evidence to show there are certain things we can do to reverse memory problems in rats."

IMPROVING MEMORY

WHERE IS ALL THIS RESEARCH LEADING? For the short term, Dr. Sutherland believes that more and more ways will be found to dramatically improve the memory of older people. "I think we'll be able to write [them] a 'prescription' for sustained good memory into their eighties and nineties. It won't be a single thing—it will be a list of ways of treating your general health, and your brain health in particular. And it will likely include therapeutic drugs. Already, for example, a University of Lethbridge spinoff company, NeuroInvestigations, Inc., is evaluating some very interesting candidates.

"Looking farther into the future, there is potential to modify progenitor cells [which are similar to stem cells] so that they will stay cycling and producing new neurons. One of the tragedies of severe age-related memory loss is that the neurons degenerate. No amount of stimulation is going to help in that situation—people would need to produce new neurons. One day, though, we may be able to predict who is at risk for problems with the hippocampus and prescribe protective factors early on.

"I'm not one who is trying to turn back the clock by stopping the process of aging. Aging is an adaptation; it has been selected to occur. Eventually medical and biomedical research will bump up against this fact. What I want to do is reduce the suffering that comes about as a result of cognitive and brain decline—to enhance enjoyment of life as long as life lasts. Memory is key to that enjoyment." *



About the researcher
AHFMR Scientist Dr. Robert Sutherland is a full professor in the Department of Psychology and Neuroscience at the University of Lethbridge, and director of the Canadian Centre for Behavioural Neuroscience.

Selected publication
Driscoll I, Howard SR, Stone JC, Monfils MH, Tomanek B, Brooks WM, Sutherland RJ. The aging hippocampus: a multi-level analysis in the rat. *Neuroscience* 2006;139(4):1173-1185.

Recommended website
NeuroInvestigations, Inc.
<http://neuroinvestigations.com>

How memories are made

Better understanding of how memories are formed could one day lead to new drugs to improve memory

MEMORIES—FOR MOST OF US, THEY'RE LIKE MAGIC. A flashback to elementary school, a snippet from an argument with a colleague, the smell of last Friday's dinner. They float up from somewhere. But where? What are they made of, and how are they actually formed? Since memory is not magic, there must be changes within brain cells that reflect the memorized element. For decades, scientists have been trying to determine the biological basis of memory.

■ "SPECTACULAR PROGRESS has been made in this area," says Heritage Senior Scholar Dr. Peter Nguyen from the University of Alberta. "One of the most important concepts

is the hypothesis that synaptic plasticity underlies memory formation."

A *synapse* is a junction between two neurons, over which chemical signals pass. *Synaptic plasticity* refers to the ability of that neuronal connection to change in strength. Long-term strengthening and weakening of the connections between neurons is believed to play key roles in how we learn and how memories are created and maintained.

"Most scientists working in this field now accept the notion that synaptic plasticity is critical for making new memories," adds Dr. Nguyen. "It makes a remarkable working platform for beginning to understand how memories are made in the human brain."

RESCUING MEMORY

ONE OF DR. NGUYEN'S PROJECTS involves studying various strains of mice that have long-term memory impairment and comparing them with mice that are not memory-impaired. His team looked at synaptic plasticity in the hippocampus and amygdala—two parts of the brain vital for making new long-term



The hypothesis is that synaptic plasticity underlies memory formation

memories. They found no difference between the two groups of mice in the initial strengthening or weakening of the connection between neurons—the memory-impaired mice, however, could not maintain the stronger connection.

"It's like having a car engine that starts well, but then conks out," explains Dr. Nguyen. "It's the only aspect of synaptic plasticity that is impaired consistently in the memory-impaired strains of mice we have examined.

"Understanding the signalling pathways that underlie synaptic plasticity gets us that much closer to understanding the cellular basis for memory," says Dr. Nguyen. That could open up the possibility of using a drug—or perhaps a substance that the body makes itself—to trigger the signalling pathways. The goal: to rescue memory in memory-impaired individuals. However, because the brain is exquisitely complex, with multiple signalling pathways that "talk" to each other, it will not be a straightforward task to develop a single "miracle" drug that enhances memory with no side effects. ✱

Related Work

The next generation of researchers > Two of Dr. Nguyen's students have followed up on his studies by discovering more about long-term potentiation (the strengthening of neuronal connections):

- AHFMR Student (M.D.-Ph.D.) Jennifer Gelinas studied beta-noradrenergic receptors. These are structures on the cell surface that trigger within the cell chain reactions (*signalling pathways*) which result in long-term strengthening of the connections between neurons. She was able to trace the pathway all the way from the surface receptor to protein synthesis within the neuron.
- Working with memory-impaired mice, then-AHFMR Student (Ph. D.) Lesley Schimanski discovered that activating the receptor chemically can enable strong long-term connections between neurons. Dr. Schimanski is now an AHFMR Fellow at the University of Arizona.



About the researcher

AHFMR Senior Scholar Dr. Peter Nguyen is an associate professor in the Department of Physiology, part of the Faculty of Medicine and Dentistry at the University of Alberta.

Selected publication

Schimanski LA, Nguyen PV. Impaired fear memories are correlated with subregion-specific deficits in hippocampal and amygdalar LTP. *Behavioural Neuroscience* 2005;119(1):38-54.

Further reading

Schacter DL. *Searching for Memory: The Brain, the Mind, and the Past*. New York: Basic Books; 1996.

Kandel ER. The molecular biology of memory storage: A dialogue between genes and synapses. *Science* 2001 Nov; 294(5544):1030-1038.

The rhythms of memory

Brain rhythms may play a role in memory storage, and in conditions such as Alzheimer's

IMAGINE THE COMPLEXITY: We have something like 100 billion brain cells—all firing at different rates and at different times in response to stimulation from the world around us as well as inside our brain. You might think the result would be a tangle of random electrical activity—but it's not. Many neurons are actually firing at the same time, creating characteristic "brain waves", and scientists can find patterns in this seeming chaos.

■ HERITAGE SCHOLAR Dr. Clayton Dickson from the University of Alberta studies these brain rhythms in the *medial temporal lobes*, which are located on either side of the brain. Deep inside each medial temporal lobe is the hippocampus. The medial temporal lobe is believed to be involved in *declarative memory*—the function of human memory that stores facts and experiences. "The human brain is a neural network of interconnected cells," says Dr. Dickson. "The neurons need to coordinate their discharges—not just for memory but for all cognitive processes. We can measure these highly coordinated patterns of activity in the brain. I want to understand more about how large sets of neurons use rhythmic electrical activity to communicate [with each other] in order to form, maintain, and retrieve memories."



These cells also have rhythmic properties

MOVING MEMORIES

ACCORDING TO ONE THEORY, although we need the hippocampus to form and retrieve new memories, we don't need it to retrieve old memories. Perhaps, after a period of time, memories are transferred out of the hippocampus, which is deep inside the brain, to the outer layers of the brain.

"One idea is that the very-low-frequency brain rhythms that we see during sleep are moving



Many neurons fire at the same time creating “brain waves”

in the brain. “So it’s possible that Alzheimer’s patients get a double whammy,” notes Dr. Dickson. “Not only are they losing important cells; they can’t generate the rhythms that may aid in memory processes.

“While we know the brain works through coordinated activity, there’s still a lot to learn about brain rhythms. I believe a better understanding will lead to more opportunities to treat devastating diseases like Alzheimer’s.” ✱

memory traces from the medial temporal lobe to the cortex,” explains Dr. Dickson. “Although there are still huge questions about neural activity during sleep, there’s no doubt in my mind that brain rhythms are the key to understanding communication between structures in the brain.”

Brain rhythms also come into play in neurological conditions such as Alzheimer’s disease. Early in the progress of Alzheimer’s, neurons in the *entorhinal cortex* are selectively destroyed; significantly, these are neurons that have intrinsic rhythmic properties. (The entorhinal cortex is located adjacent to the hippocampus and is the major source of input to the hippocampus.) Other nerve cells that are destroyed in Alzheimer’s patients are *cholinergic neurons*, and these are cells that play a role in setting up different rhythms



About the researcher

AHFMR Scholar Dr. Clayton Dickson is an associate professor in the Department of Psychology, part of the Faculty of Science at the University of Alberta.

Selected publication

Wolansky T, Clement EA, Peters SR, Palczak MA, Dickson CT. Hippocampal slow oscillation: a novel EEG state and its coordination with ongoing neocortical activity. *Journal of Neuroscience* 2006 Jun 7;26(23):6213–6229.

Further reading

Buzsáki G. *Rhythms of the Brain*. Oxford; New York: Oxford University Press; 2006.

The Alzheimer's puzzle

Alzheimer's disease takes a tremendous toll on individuals suffering from it as well as their families. Protecting against the loss of nerve cells could hold the key to helping thousands.



THE NUMBERS behind Alzheimer's disease are not comforting. An estimated 290,000 Canadians over 65 have Alzheimer's and its prevalence is increasing.

■ "ALZHEIMER'S affects not only the individual with the disease; there's an enormous burden of care on the family," says Heritage Senior Scholar Dr. Satyabrata Kar, a neuroscientist with the Centre for Alzheimer and Neurodegenerative Research at the University of Alberta. "I am aware of the magnitude of suffering caused by this disease. As a researcher, I am trying to understand the cause of the disease and how it can be treated effectively."

THE LOSS OF NEURONS

DR. KAR'S RESEARCH focuses on the characteristic loss of neurons in Alzheimer's—particularly, a group of *cholinergic neurons* that are affected selectively in the brains of patients suffering from Alzheimer's disease. These neurons use a chemical called *acetylcholine* to transmit signals

How do drugs for Alzheimer's actually work in the brain?

to other neurons or cells in the body. Because cholinergic neurons are responsible for such cognitive functions as reasoning and remembering, their death causes memory loss and reduced ability to think. "I want to understand why these neurons are dying and what can be done to protect them," explains Dr. Kar.

One way to do this is to study how drugs for Alzheimer's actually work in the brain. Dr. Kar's team studies drugs that are being developed, as well as drugs that are already approved for the treatment of Alzheimer's. Currently his team is investigating memantine, a new Alzheimer's drug that is showing positive results in patients.

"Although this drug was not designed to protect the cholinergic neurons, it seems to be having a protective effect," notes Dr. Kar, "So we need to understand the underlying mechanism of its action. Knowing how a drug stops or slows down neurodegeneration gives us clues to the biologic events that precede neurodegeneration. That knowledge can be used by others to improve the drug or develop new drugs. We're trying to solve a puzzle." *



About the researcher
AHFM Senior Scholar
Dr. Satyabrata Kar
is an associate professor in the departments of Medicine and Psychiatry at the University of Alberta.

Selected publication
Kar S, Slowikowski SPM,

Westaway D, Mount HTJ. Interactions between β -amyloid and central cholinergic neurons: implications for Alzheimer's disease. *Journal of Psychiatry and Neuroscience* 2004;29(6):427-441.

Recommended website
Alzheimer Society Canada
<http://www.alzheimer.ca>

Alzheimer's disease



Alzheimer's disease is an age-related disease that attacks the brain and is the most common cause of dementia. Three key changes can be seen

in the brain tissue of people who had Alzheimer's disease:

- There are many fewer nerve cells (neurons) and the connections between them (synapses) than in a healthy brain.
- Abnormal clusters of protein fragments have built up between the cells, interrupting communication between them.
- Cells that were dead or dying contain tangles of twisted protein strands.

Related Work

Centre for Alzheimer and Neurodegenerative Research

The Centre for Alzheimer and Neurodegenerative Research (CANR) at the University of Alberta is a research centre for the study of Alzheimer's disease and related neurodegenerative conditions, such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS).

See <http://www.canr.ualberta.ca/> for more information.

Community, collaboration, and older adults

Aging "in place", in your own neighbourhood, is finally becoming a real choice, thanks to Calgary's Elder Friendly Communities Program.



THE ELDER FRIENDLY COMMUNITIES PROGRAM, which celebrated its fifth anniversary in November 2006, is shaping the future look of communities for older adults.

This made-in-Alberta initiative unites older adults and the professionals who serve them in a common goal: to improve the quality of life for older adults in their own communities. Five Calgary neighbourhoods and two cultural communities are experiencing the benefits that even the smallest adjustments can bring. Tai Chi classes, health presentations, potluck dinners, inter-generational programs linking older adults with school-age children, and yard-care or snow-removal services all help create friendlier, healthier, and more fulfilling places to live.

"Aging is a universal experience—if we're lucky"

Dr. Carol Austin, a gerontologist and professor of social work at the University of Calgary, was the lead investigator for AHFMR-supported research into two of the program's processes: collaboration between support organizations, and the development of communities for older people. "Aging is a universal experience—if we're lucky," says Dr. Austin. "But many older adults of sound mind and body are not sufficiently engaged or recognized for skills they have developed over the years."



Elder-friendly communities do things *with* older adults, not *to* them, helping them age "in place"—in their own homes and neighbourhoods. Needs are determined by the older adults themselves, not by the professionals and organizations serving them. Since experts are used to doing things to others, this supportive role is a major operational shift for professional practitioners. It's also a refreshing change, especially for the older adults.

A transformation like this doesn't happen in isolation. Dr. Austin worked alongside two academic researchers, Dr. Jackie Sieppert and Dr. Robert McClelland, and research coordinator Ellen Perrault, as well as several partnering organizations, professional practitioners, and older adults. The goal was to promote vital involvement and civic engagement in elder-friendly communities.

According to Dr. Austin, partnerships and collaborations are standard requirements for



Elder-friendly communities can improve quality of life for older adults

addressing complex issues today. But, she says, it's much easier said than done. Collaboration is why the Elder Friendly Communities Program is a success. "Collaborative skills are often unrecognized or under-appreciated. You must spend time and money to develop meaningful, long-term collaborative relationships."

One collaboration worthy of special note is one with the University of South Australia. Based on the Calgary program, visiting professor Di Gursansky started the enormously successful West Adelaide Elder Friendly Communities Project. "It's not every day that an Alberta-made program gets adopted as public policy somewhere else [halfway] around the world," points out Dr. Austin.

The South Australia government has recognized aging as one of the most significant social trends of our time. It has embraced the findings of the Elder Friendly Communities Program

Elder Friendly Communities Program collaborators

Key program collaborators include Calgary Family Services Society, the Calgary Health Region, The City of Calgary Seniors Services Division, and the Faculty of Social Work at the University of Calgary. These organizations have been on board since the program's inception, providing extraordinary stability in the group and constituting its steering committee. The Calgary Catholic Immigration Society and Jewish Family Services Calgary have joined the collaboration more recently.

in the most concrete of ways—with financial support that will be used to develop other projects based on the West Adelaide experience.

Back in Canada, the intertwining of research and program implementation represents a unique, working marriage between academia and the "real world". As a result, Alberta's Elder Friendly Communities Program has become a poster child for community collaboration, one from which many disciplines—including seniors care—could learn.

The next big challenge facing Dr. Austin and her team is to share their research findings with both academic and non-academic audiences far and wide. It will be useful to older adults, community workers, and commercial operations all around the world. *



Dr. Carol Austin with collaborators Dr. Robert McClelland (L) and Dr. Jackie Sieppart (R)

About the researcher

Dr. Carol Austin

is a full professor in the Faculty of Social Work at the University of Calgary. Her work on the Elder Friendly Communities project was supported through the *Health Research Fund*, administered by AHFMR on behalf of Alberta Health and Wellness.

Recommended website

Elder Friendly Communities Program

<http://www.elderfriendlycommunities.org>



How children learn

AHFMR Student Samantha Nayer studies how language helps children learn about their world.



INFANTS AND TODDLERS understand much more than we give them credit

for, says Calgary researcher Samantha Nayer.

"We tend to underestimate how much infants and children really know," she explains. "The more we develop new technology for investigating infants' understanding, and the more we do research, the more we realize that infants develop abilities a lot earlier than most adults think they do."

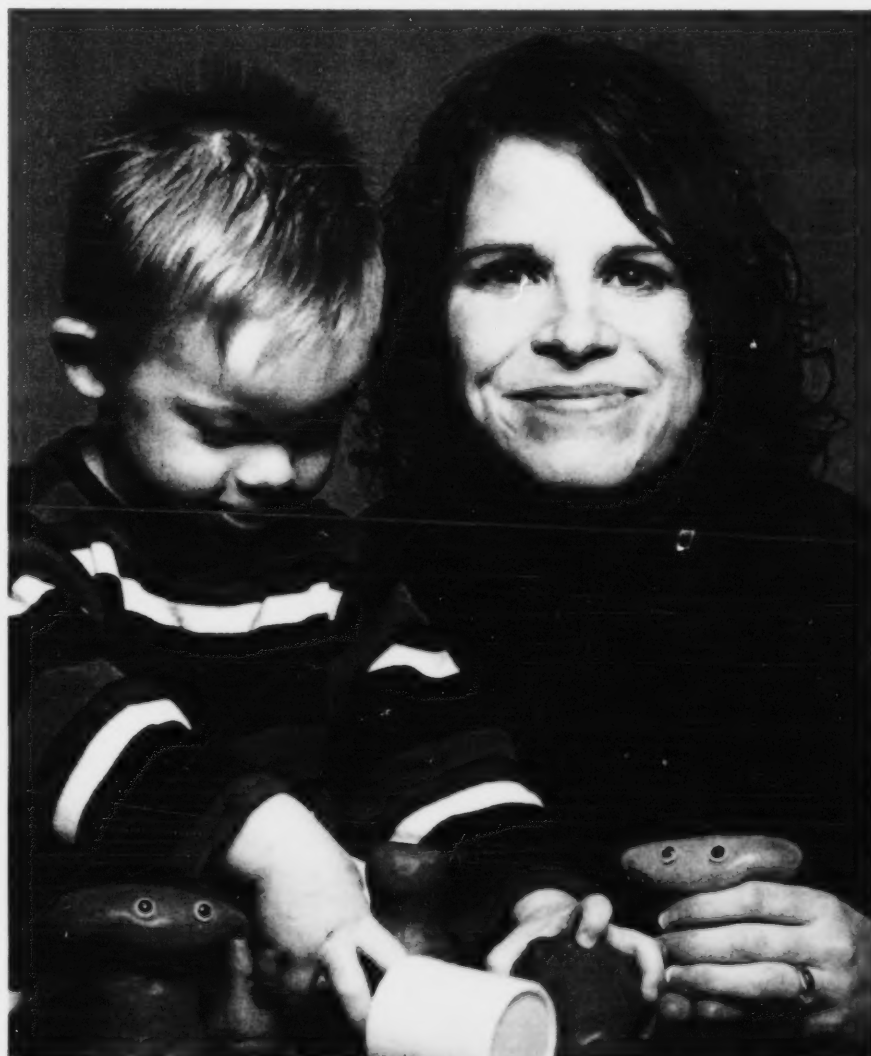
Infants and young children learn very quickly and very efficiently before they receive any formal education in school, suggests Nayer. For example, babies are able to understand language long before they can produce language. As a matter of fact, researchers have discovered that children typically know about 10,000 words by the time they enter Grade 1.

Nayer, a Heritage doctoral student in clinical psychology,

is fascinated by normal language development in infants and toddlers (how they acquire language). She also investigates their normal cognitive development (how they understand the world around them) and theory

of mind development (how they understand other people's mental states).

For her master's research Nayer investigated how children adapt the way they communicate according to what the person listening to them knows. Using a word-learning task and a toy-retrieval game as assessment tools, she found that, by the age of three, children usually understand that they should change how they talk to someone in line with what that person knows



Nayer studies how young children interpret language

Babies understand language long before they produce language

or doesn't know about a given situation. Before the age of about two and a half, they think that whatever they see or know is what everybody sees or knows. For example, toddlers talking on the phone think that the person they are talking with can see what they see.

"Theory-of-mind understanding is actually one of the very important abilities that's missing from children with autism or a condition called Asperger's syndrome," she explains. "They have difficulty interpreting others' mental states or emotions. It's very important for us to figure out the development pattern of a typical child so that we can target, diagnose, and treat the atypical child."

For her Ph.D. research, Nayer has been investigating language and cognitive development—how language helps toddlers learn about the world around them. For instance, she studies how young children interpret language ("Dogs wag their tails") to help them learn whether a specific property (tail-wagging) is characteristic of a given category (dogs).

"One of my biggest passions in this area—what really keeps me going and interested—is just how unbelievably proficient these young children are

at learning words and learning about the world around them," she says. "They learn so rapidly, yet we are still a bit puzzled as to how."

Another reason why Nayer enjoys her work so much is that researchers need to be innovative when working with infants and toddlers in order to find ways to tap into their knowledge. "It's really interesting and challenging research. We can't sit down with infants and ask them what they're thinking, or give them a questionnaire and ask them what's going on in their head," she explains. "In our lab we've developed very creative, fun, interactive games to play with the children. The children really enjoy it."

"I have two separate career goals," she says. "I would like to be a clinical researcher investigating atypical child development. I would also like to work in the public sector assessing, diagnosing, and treating mental health disorders in children. Ideally I would love to work as a health psychologist helping children who have mental-health concerns, such as depression, as well as physical-health conditions, such as cancer." *

About the researcher
Samantha Nayer is an *AHFMR Student* working toward a Ph.D. in clinical psychology at the University of Calgary.

AHFMR funding partners

The Alberta Heritage Foundation for Medical Research (AHFMR) has

contributed more than \$850 million to Alberta's health-research community. The Foundation also relies on the contributions of many partners in building and sustaining health research in this province. To mention just a few, these partners include

- the Government of Alberta and its related ministries and programs;
- federal granting agencies such as the Canadian Institutes of Health Research, the Canada Foundation for Innovation, and the Canadian Health Services Research Foundation;
- international funding partners like the Wellcome Trust and the National Institutes of Health; and
- non-profit and voluntary funding agencies such as NeuroScience Canada, the Heart and Stroke Foundation, the Canadian Diabetes Association, and the National Cancer Institute of Canada.

Following up

Research News checks in with two clinical dietitians on their work to prevent eating disorders in children.



Suzanne Hare (L) and Dianne Drummond (R)

■ THE MEDIA bombard us constantly with images of glamorous actors and models and their seemingly perfect bodies. These images take their toll. Most of us have felt the pressure to attain those impossible standards of beauty. So it should come as no surprise that these expectations also affect our children.

Clinical dietitians Dianne Drummond and Suzanne Hare have seen that fallout up close. *Research News* first featured the two in the Fall 2001 issue, as they embarked on a wellness program aimed at preventing eating disorders among 700

Edmonton students in grades 5 and 7. The program saw the kids complete tests to evaluate their general health-related behaviour, their body image, and their attitudes toward eating and weight. Further assessments measured peer influence and the children's perception of the stress in their lives.

Overall incidence of eating disorders was 19%

The eye-opening results found everything from dieting and compulsive overexercising to bingeing and purging. The overall incidence of eating disorders among these students was 19%—a shock to parents who thought their fifth-grade kids were too young to worry about such things. And boys have just as many body issues as girls do. “Boys want to be bigger and more muscular, whereas girls want to be smaller and slimmer,” explains Hare.

The good news? The wellness program changed the children's knowledge of, and attitudes toward, weight and shape. The

biggest improvement was seen among Grade 5 boys. The less good news? While behaviour did generally improve, the program didn't result in changes which could be called significant—changing behavior being a much more complicated task than simply changing attitudes.

“Changing behaviour will likely require a great deal of reinforcement—in the curriculum and elsewhere—of the program's messages about healthy practices,” says Drummond. Since eating disorders typically surface in junior high school, prevention programs are needed for younger kids, whose behaviour is easier to change. The two dietitians now hope to develop their program to form part of the regular school curriculum. ✱

About the researchers

Dianne Drummond is the Eating Disorder Promotion and Prevention Specialist for Capital Health. **Suzanne Hare** is a clinical dietitian at the Grey Nuns Hospital. Their study was supported through the *Health Research Fund*, administered by AHFMR on behalf of Alberta Health and Wellness.

